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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/954,954	10/21/1997	NEENA L. SUMMERS	2991/1	6756

7590 06/25/2004

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/954,954	SUMMERS ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The response received 10 May 2004 has been entered in full. No claims have been amended or canceled. Claims 1-14 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. § 103

Claims 1, 5 and 10-14 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Pastan et al. (U.S. Patent 5,635,599) in view of Wen et al. (1993, Blood 82:1507-1516). The basis for this rejection is set forth at pp. 2-5 of the previous Office Action (mailed 08 January 2004).

Claims 1-4 and 6-9 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Pastan et al. (U.S. Patent 5,635,599) in view of Wen et al. (1993, Blood 82:1507-1516) as applied to claims 1, 5 and 10-14 above, and further in view of Chaudhary et al. (1989, Nature 339:394-397) and Cousens et al. (U.S. patent 4,751,180). The basis for this rejection is set forth at pp. 5-6 of the previous Office Action (mailed 08 January 2004).

Applicant's arguments (pp. 2-4, response received 10 May 2004) have been fully considered but are not found to be persuasive for the following reasons.

Applicant argues that the rejection is flawed because Pastan et al. do not teach the selection of an opening site through a comparison of the non-conserved amino

acids of a single protein as found native in multiple biological species. Applicant characterizes Pastan et al. as suggesting that a good candidate for an opening site can be found in a region of non-conserved amino acids where the protein is a member of a family of related, but different, proteins. Applicant argues that Wen et al. do not provide a comparison of members of a family of proteins, but compare a single protein found in different species. This has been fully considered but is not found to be persuasive. Pastan et al. teach that the opening site must be in a place that is not critical for biological activity (column 7, li. 8-11). Pastan et al. teach that highly conserved sequences are critical for biological activity, stating that "where the substitutions of certain amino acids ... does not change the activity of a protein, it is expected that the modified amino acids are not critical to the protein's activity" (col. 8, li. 30-35). The alignment of EPOs from different species by Wen et al. provides the skilled artisan with exactly that information. See Wen et al., abstract, wherein it is stated that the purpose of the research was to investigate structure-function relationships. Wen et al. speak of amino acid substitutions, deletions, and/or insertions as occurring between the sequences during evolution (abstract). Therefore, Wen et al. provide precisely the information Pastan et al. deem important in choosing an opening site. Furthermore, Pastan et al. speak about comparisons of homologous proteins (col. 8, li. 50-53), which are the type of proteins compared by Wen et al. Note the definition of homologous proteins provided by Life Sciences Dictionary: "proteins that look similar and work in similar ways *in different species*" (emphasis added). This is precisely what Pastan et al. suggest and Wen et al. provide. Finally, even if Pastan et al.'s teachings can be

construed to be limited to comparisons of different proteins belonging to the same family in one species, the skilled artisan would immediately recognize that a comparison of the same protein across different species would give even more specific information regarding preferred opening sites, as there would be greater conservation of sequences between the single protein across different species, and those proteins all share the same function. Such is not always true of different proteins belonging to a protein family.

Applicant also argues that Pastan et al. do not teach that breakpoints can be found at single non-conserved amino acid positions, but limit their teachings to stretches of amino acids at least 5 amino acids in length. Applicant characterizes Pastan et al.'s teachings as being limited to a suggestion that a breakpoint can be found within the region. Applicant concludes that Pastan et al. suggests looking at sites within a region that are conserved among protein families. This ahs been fully considered but is not found to be persuasive. Applicant mischaracterizes the disclosure of Pastan et al. The last paragraph of col. 8 and the first paragraph of col. 9 of Pastan et al. discuss how sequences are aligned to look for conserved and non-conserved regions. The 5, 10 or 50 amino acids discussed by Pastan et al. are the "window sizes" that are set within the alignment programs. The next paragraph discusses how the optimal opening sites for IL4 are between amino acids 37 and 38 and between amino acids 104 and 105. Similarly, opening sites between 2 contiguous amino acids for IL2, G-CSF and GM-CSF are disclosed. It is implied that an alignment provided this information regarding precise amio acid positions, not regions of at least 5 amino acids in length. Also, at col. 8, lines

35-39, Pastan et al. state that, "...amino acids that are either known to be susceptible to modification or are actually modified in vivo are potentially good candidates for opening sites. For example, residues 38 and 105 of IL4..." Clearly, Pastan et al. is pointing to specific amino acids, not longer regions.

Applicant argues that neither Pastan et al. nor Wen et al. teach or suggest that the protein activity of EPO will remain unaltered if any amino acid is substituted. This has been fully considered but is not found to be persuasive. See Wen et al., abstract, wherein amino acid substitutions, deletions and/or insertions are discussed. See also p. 1514, top of left column. Wen et al. are speaking of the substitutions, deletions and/or insertions that occur during evolution, as species evolve from one another and a common ancestral protein. All of the EPO proteins disclosed by Wen et al. are active, and have the same EPO function. Therefore, the information provided by Wen et al. provides the exact information Pastan et al. deem important for determining opening sites: which amino acid residues can tolerate substitution, deletion and/or insertion without resulting in loss of the protein's activity.

Applicant argues that Wen et al. state that information involving the three-dimensional structure of EPO is not available and that the amino acid sequence of Wen et al. are merely predicted. This has been fully considered but is not found to be persuasive. In Figure 6A of Wen et al., the location of four alpha helices is clearly indicated. This is the sort of three-dimensional structural information that Pastan et al., and even the instant specification, indicate as important information for determining potential opening sites. Finally, several amino acid sequences of Wen et al. are

predicted, using data from the DNA sequencing. The amino acid sequences are not completely hypothetical. They are predicted from the genetic code common to all higher organisms.

Applicant argues that Chaudhary et al. and Cousens et al. are directed to fusion proteins and not circularly permuted molecules. Applicant argues that the linkers of Chaudhary and Cousens prevent two fused proteins from interfering with each other whereas the linkers of circular permuteins are used to properly position the amino acids on either side of the linker, allowing for proper folding. Applicant concludes that there is no motivation for one skilled in the art to combine the teachings of Chaudhary et al. and Cousens et al. with Pastan et al. or Wen et al. This has been fully considered but is not found to be persuasive. The linkers of Chaudhary et al. and Cousens et al. are Gly-Ser rich, allowing for flexibility. Such are the type of linkers suggested by Pastan et al., and used in the instant specification and claims.

35 U.S.C. § 112, First Paragraph

Claims 1-14 remain rejected under 35 U.S.C. § 112, first paragraph, for scope of enablement as set forth at pp. 6-9 of the previous Office Action (mailed 08 January 2004).

Applicant's arguments (pp. 4-6, response received 10 May 2004) have been fully considered but are not found to be persuasive for the following reasons.

Applicant argues that the test for enablement of the claimed methods of use is undue experimentation, not proof of biological activity, efficacy, safety or other utility.

Applicant reviews the Wands factors. The examiner takes no issue with this. The previous Office Action carefully reviewed the Wands factors and concluded that undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Applicant argues that the specification enables each of the claimed polypeptides and provides support for making and using them. Applicant argues that the amount of guidance in the specification is sufficient for one skilled in the art. Applicant points to specific places in the specification as supporting this. Applicant argues that the breadth of the claims is limited as there are a finite number of molecules claimed. Applicant argues that no working examples are required. Applicant concludes that the specification teaches one skilled in the art how to make and use the claimed polypeptides, and that there is no doubt as to the truth of the statements in the specification. This has been fully considered but is not found to be persuasive. As discussed in the previous Office Action from pp. 8-9, the Wands factors indicate that undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope. A large amount of experimentation would be required to make the extremely large number of EPO circular permuteins encompassed by the claim and test them for EPO activity. The specification provides limited guidance regarding the opening sites recited in the claim other than to provide a list of them and state that they are appropriate. There is very limited guidance regarding what combinations of opening sites, linkers, and EPO starting sequence will result in proteins having the activity recited in the claims. There are no working examples. While it is

true that working examples are not required, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The nature of the invention is extremely complex. Prediction of tertiary protein structure from a primary amino acid sequence generally takes complicated computer programs that are not always accurate, combined with crystallography research. After that, function has to be tested. In the claimed circular permuteins, there are different regions that are interacting together: the two parts of the circular permutein and the linker. The state of the prior art indicates that only certain amino acids may be potential opening sites (i.e., Pastan et al. combined with Wen et al.). The effects of mutation, such as circular permutation and addition of linkers, on the overall protein's function are highly unpredictable. Finally, the breadth of the claims is quite large, starting with several choices for the EPO starting sequences, several potential opening sites, and several, if not an infinte number of, possible linker sequences. In view of these considerations of the Wands factors, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ECK

ELIZABETH KEMMERER
PRIMARY EXAMINER